Combined preconditioning and in vivo chemoselection with 6-thioguanine alone achieves highly efficient reconstitution of normal hematopoiesis with HPRTdeficient bone marrow.

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Authors: K Hacke, A Szakmary, A R Cuddihy, N Rozengurt, N A Lemp, J Aubrecht, G W Lawson, N P Rao, G M Crooks, R H Schiestl, N Kasahara

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Public Summary:
In order to transplant stem cells in the bone marrow from one person to another, generally it is current practice to destroy the recipient's bone marrow first, to make space for the donor cells to engraft. However, this requires "conditioning" of the recipient's bone marrow with radiation or chemotherapy drugs resulting in considerable toxicity, and frequently is not well tolerated. Here we have developed proof-of-concept for a new approach to use genetically modified bone marrow stem cells that are naturally resistant to the effects of a mild chemotherapy drug. By giving the drug just before transplantation, and continuing drug administration for several weeks, even with a small number of donor cells it is possible to gradually turn over the recipient's bone marrow so that the donor cell population can be selectively expanded after transplantation. This represents a highly efficient new method for both efficient engraftment and to selectively increase the number of transplanted stem cells after transplantation, with little or no toxicity.

Scientific Abstract:
Purine analogs such as 6-thioguanine (6TG) cause myelotoxicity upon conversion into nucleotides by hypoxanthine-guanine phosphoribosyltransferase (HPRT). Here we have developed a novel and highly efficient strategy employing 6TG as a single agent for both conditioning and in vivo chemoselection of HPRT-deficient HSC. The dose-response and time course of 6TG myelotoxicity were first compared in HPRT-wild type mice and HPRT-deficient transgenic mice. Dosage and schedule parameters were optimized to employ 6TG for myelo-suppressive conditioning, immediately followed by in vivo chemoselection of HPRT-deficient transgenic donor bone marrow (BM) transplanted into syngeneic HPRT-wild type recipients. At appropriate doses, 6TG induced selective myelotoxicity without any adverse effects on extra-hematopoietic tissues in HPRT-wild type mice, while HSC deficient in HPRT activity were highly resistant to its cytotoxic effects. Combined 6TG conditioning and post transplant chemoselection consistently achieved approximately 95% engraftment of HPRT-deficient donor BM, with low overall toxicity. Longterm reconstitution of immunophenotypically normal BM was achieved in both primary and secondary recipients. Our results provide proof-of-concept that single-agent 6TG can be used both for myelo-suppressive conditioning without requiring irradiation, and for in vivo chemoselection of HPRT-deficient donor cells. Our results show that by applying the myelosuppressive effects of 6TG both before (as conditioning) and after transplantation (as chemoselection), highly efficient engraftment of HPRT-deficient hematopoietic stem cells can be achieved. HACKE et al. 6TG IN VIVO CHEMOSELECTION 4.